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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER |
|---|
| GARVEY, TARA L |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

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DATE MAILED: 09/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/089,278 | CICHUTEK ET AL. | |
| | Examiner | Art Unit | |
| | Tara L. Garvey | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,7 and 8* is/are rejected.

7)☒ Claim(s) *1-3 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/29/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-10 are pending.

### *Election/Restrictions*

Claims 9 and 10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 15, 2005.

Applicant's election with traverse of Group I in the reply filed on August 15, 2005 is acknowledged. The traversal is on the ground(s) that Groups I and VI are linked to form a single general inventive concept. This is not found persuasive because a special technical feature does not exist between the different methods of the two groups since each method contains steps not present in the other methods

The requirement is still deemed proper and is therefore made FINAL.

### *Information Disclosure Statement*

The IDS submitted on October 29, 2003 was received and considered except for one citation. Foreign patent document DE 197 52 854 A1 is entirely in German and could not be considered.

### *Specification*

The first paragraph of the specification was amended in a preliminary amendment filed on March 26, 2003 to claim priority to PCT/DE00/3444, but the claim to priority should state that "This application is a 371 of PCT/DE00/3444 filed on September 27, 2000".

### *Claim Objections*

Claims 1 and 2 are objected to because of the following informalities: Sequence identifiers are needed to describe the claimed sequence present in Figure 1. A suggestion would be to replace the "according to any of the figures 1-5" with "of SEQ ID NO: 6". Appropriate correction is required.

Claim 3 is objected to as being dependent upon an objected base claim.

Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, relative skill in the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claim, with the most relevant discussed below.

*Nature of the invention:* The claims are directed to a gene therapy method using a cell targeting vector that is derived from spleen necrosis virus and encodes a single chain variable fragment (scFv) and a pharmaceutical composition of the cell targeting vector.

*Guidance in the specification and existence of a working example:* The specification does not show any success in treating any disorder by using the method of gene therapy or DNA vaccination. The working examples describe the transduction

efficiency of a cell targeting vector in T cells of only 20%. The *in vitro* data cannot be used to predict what will occur *in vivo*. The specification does not contain any teachings that address the ability of the composition to treat a human subject or even its ability to target cells *in vivo*. Specifically, the specification has not taught an appropriate tested dose for humans, the amount of therapeutic gene expression necessary for successful treatment, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. The lack of guidance would require trial and error experimentation to determine these factors.

*State of the art and predictability of the art:* At the time of filing, the prior art demonstrates that treating a disease by a method of gene therapy was not routine. Gene therapy using administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods had not seen any success despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells-and getting them expressed-remain a nagging problem for the entire field", and that "many problems must be solved before gene therapy will be useful for more than the

rare application" (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-Hill, NY) explains, "the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al, bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al teaches, in reference to *ex vivo* methods, that weak promoters produce only low levels of therapeutically effective protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of

therapeutically effective protein be achieved (Verma et al, *supra*, page 240, column 2). Verma et al further warns that, "...the search for such combinations is a case of trial error for a given cell type" (Verma et al, *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al, Human Gene Therapy,1996, Volume 7, pages 1781-1790, see page 1789, column 1, first paragraph). Thus, the art at the time at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142) teaches that the problems described above remain unresolved. Rubanyi states, "[a]lthough theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see "3. Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression.

Specifically in terms of therapeutic use of cell targeting vectors based on SNV, Karavanas et al mentions that SNV-based vectors expressing a scFv may be an alternative to the inefficient MLV-derived vectors for targeted infection, but further concludes that "major improvements in technology are thus required before any *in vivo* application, both in animals and humans, can be envisaged" (Critical Reviews in Oncology and Hematology (1998) volume 28, pages 7-30, see page 16, right column, last paragraph bridging page 17, left column and page 18, right column paragraphs 1-3 bridging page 19 to top of right column). Furthermore, at the time of the applicant's filing of the instant application, clinical application of an SNV-based vector system was still in the development stages. A human packaging cell line for an SNV system was still needed to facilitate translation to the clinical setting (Galanis et al. Critical Reviews in Oncology and Hematology (2001), volume 38, pages 177-192, see page 180, right column, last paragraph bridging page 181, top of left column and page 181, left column, last paragraph bridging right column). Finally, post-filing art describes that the therapeutic use of SNV-based vectors for a disorder such as HIV-1 have not yet been examined. Marusich et al describes that prior to the use of SNV-based viral vectors for therapeutic gene delivery a number of areas should be researched such as vector- host interactions, viral particle transport, persistence of viral DNA and pre-clinical studies in large animal models to determine the efficacy of the SNV vector *in vivo* (Virology (2005) volume 323, pages 258-271, see page 267, right column, first-third full paragraphs). Thus, as of the filing date of the instant application, gene therapy was regarded as unsuccessful and unpredictable.

*Quantity of experimentation:* The art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease. The skilled artisan would not be able to use the cell targeting vector in the instant claims to treat a disease such as a T cell specific disorder without a large amount of trial and error experimentation to determine ways to target cells efficiently *in vivo* and to achieve expression levels necessary to be sufficient for a therapeutic effect.

*Conclusion:* In order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to achieve effective levels of the expressed protein, to select a proper dose or administration route or to determine other factors for a successful treatment. The prior art did not compensate for the lack of guidance in the specification since the teachings do not recognize any clearly successful gene therapy methods. The skilled artisan would have had to engage in a large amount of experimentation to practice the claimed invention. In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 4 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the claimed subject matter are not defined. The phrase "derived from" is unclear because it does not distinguish from where it is derived and does not define the scope of the limitations.

Claim 8 provides for the use of a cell targeting vector but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 8 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tara L Garvey whose telephone number is (571) 272-2917. The examiner can normally be reached on Monday through Friday 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tara L Garvey
Examiner
Art Unit 1636

TLG

JAMES KETTER
PRIMARY EXAMINER